CONCISE COMMUNICATION

Worldwide Incidence of Multidrug-Resistant Tuberculosis

Christopher Dye, Marcos A. Espinal, Catherine J. Watt, Cyrille Mbiaga, and Brian G. Williams

Communicable Diseases, World Health Organization, Geneva, Switzerland

Planning for tuberculosis (TB) control requires an assessment of the number and distribution of drug-resistant cases. This study used results of resistance surveys from 64 countries, together with data predictive of resistance rates from 72 others, to estimate the number of new multidrug-resistant (MDR) TB cases that occurred in 2000. By these methods, an estimated 273,000 (95% confidence limits, 185,000 and 414,000) new cases of MDR TB occurred worldwide in 2000, 3.2% of all new TB cases. The analysis provides the first comprehensive set of estimates of the MDR TB burden by country and globally.

The most important measure of tuberculosis (TB) drug resistance is the number of new cases that are resistant to at least isoniazid and rifampicin. The treatment of such multidrug-resistant (MDR) TB cases requires a departure from standard short-course regimens. Moreover, multiple resistance among new cases means not simply that resistance has been acquired through treatment failure but also that the resistant strains have generated new cases following transmission.

In surveys of sputum smear–positive TB patients in 64 countries [1, 2], an average of 3.4% (weighted by incidence in each country [3]) of new cases had MDR TB (table 1). New cases were patients who, in response to direct questioning, denied prior treatment or treatment for ≥ 1 month and who had no documented history of treatment [2]. The highest rates were in Estonia (14%), Henan Province, China (11%), Latvia (9%), and Ivanovo (9%) and Tomsk (7%) oblasts, Russia. The countries taking part in these surveys were not selected so as to represent the worldwide distribution of drug resistance, so we cannot assume that the 3.4% average applies globally. To obtain a better estimate, we used the survey data and multiple logistic regression analysis to identify a set of variables that can predict the number of MDR TB cases in countries where no resistance surveys have yet been carried out.

Methods

Our general approach was to identify a set of independent widely measurable variables predictive of MDR TB rates by use of data collected from the 64 surveyed countries. We used the resulting regression equation, together with measures of the independent variables, to estimate MDR TB rates in 72 more countries. These 136 countries have 97% of the world's population.

For both surveyed and nonsurveyed countries, we had measures of 7 independent variables that a priori are likely to be associated with resistance: number of years of rifampicin use [1, 2]; whether drugs were administered in fixed-dose combinations [1, 2]; estimated TB incidence rate (as ln incidence/person/year) [3, 4]; percent of patients receiving short-course chemotherapy [1, 2]; percent successfully treated [1, 2]; percent previously treated [1, 2]; and percent coinfected with human immunodeficiency virus [1, 2]. We also included 2 indicators that might be linked indirectly to the distribution of resistance: gross national product (expressed as ln GNP) [5] and region of the world (8 areas) [3]. From this list we selected the variables with significant predictive power by using χ^2 as a criterion for backward elimination in multiple logistic regression [6].

One strength of this approach is that it allows explicit calculation of the SEs on estimates of MDR TB incidence. The errors come from 3 sources. For countries that have surveyed the proportions of TB cases carrying MDR TB, there are errors due to the finite sample sizes of the surveys (binomial errors on proportions) and to uncertainties surrounding estimates of the number of TB cases [4]. If n_i is the total number of tuberculosis cases in country i and p_i is the proportion that are MDR, then the total number of MDR TB cases is $m_i = n_i p_i$, and the variance is

$$\frac{V(m_i)}{m_i^2} = \sum \left[\frac{V(n_i)}{n_i^2} + \frac{V(p_i)}{p_i^2} \right].$$

The total for the surveyed countries is obtained by summing the 64 country estimates, and the variance of this total is the sum of the country-specific variances.

The regression analysis introduces a third source of error that applies to the estimates for nonsurveyed countries. This error can be evaluated as follows. Let the proportion of drug-resistant cases measured for a particular country be $\hat{p}(x)$ with $x = (A, B, C, \ldots)$. Because the regression is done on logistically transformed data, the observed y values are $\hat{y} = \ln[\hat{p}/(1 - \hat{p})]$. The coefficients of $(A, B, C, \ldots)$ are the elements of a vector $\boldsymbol{\alpha}$, the covariance matrix of the coefficients is $\mathbf{C}(\boldsymbol{\alpha})$, and the covariance matrix of the estimates of the fitted

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Reprints or correspondence: Dr. C. Dye, Communicable Diseases (L51), World Health Organization, 1211 Geneva 27, Switzerland (dyec@who.int).

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Table 1. Estimated numbers and proportions of multidrug-resistant (MDR) tuberculosis (TB) cases in surveyed and nonsurveyed countries and by geographic region.

Geographic region	No. of MDR TB cases (% of all new cases)	Low 95% CL (% of all new cases)[a]	High 95% CL (% of all new cases)[a]
All countries ($n = 136$)	272,906 (3.2)	184,948 (2.6)	414,295 (3.9)
Surveyed countries ($n = 64$)	166,276 (3.4)	111,544 (2.7)	253,136 (4.2)
Nonsurveyed countries ($n = 72$)	106,630 (3.0)	56,421 (1.8)	172,899 (4.2)
Established market economies[b]	882 (0.7)	121 (0.1)	1723 (1.3)
Latin America	8508 (2.2)	4347 (1.3)	13,913 (3.1)
Eastern Europe	17,269 (5.5)	8745 (3.2)	28,302 (7.8)
Africa, low HIV	15,014 (1.9)	4083 (0.6)	27,527 (3.3)
Africa, high HIV	25,199 (1.8)	12,579 (1.0)	41,439 (2.6)
Eastern Mediterranean	45,964 (7.9)	8128 (1.7)	88,144 (14.1)
Southeast Asia	75,062 (2.5)	35,369 (1.3)	125,088 (3.7)
Western Pacific	85,008 (4.5)	58,327 (3.7)	128,607 (5.4)

NOTE. HIV, human immunodeficiency virus.

[a] 95% Confidence limits (CLs) on percentages include errors due to survey sample sizes and from regression analysis; 95% CLs on numbers include errors associated with estimating TB incidence.

[b] Countries in each region are from [3]. Estimates for all countries are shown in table 2.

points $\mathbf{y}$ is $\mathbf{C(y)} = \mathbf{x}^t\mathbf{C}(\boldsymbol{\alpha})\mathbf{x}$, where t indicates the transpose of the matrix. To get the covariance matrix of the fitted proportions, $\mathbf{p(x)}$, we use the linear term in a Taylor expansion to obtain $\mathbf{C(p)} = \mathbf{F}^t\mathbf{C(y)F}$, where

$$\mathbf{F}_i = \left| \frac{dp}{dy} \right|_{y_i}.$$

Then this third source of variation in the estimated number of MDR cases *(E)* arising from the regression is

$$V(E) = \sum_{i,j} n_i n_j C(p_i, p_j)$$

and is computed with data from all pairs of countries i, j. To calculate the total error on estimates for 72 nonsurveyed countries, $V(E)$ must be added to the average variance of the point estimates for the surveyed countries and, as above, the variance associated with estimates of the numbers of TB cases.

Results

Logistic regression analysis of data from the 64 surveyed countries yielded 3 variables (treatment success *[T],* ln GNP *[G],* and geographic region) that together explained 44% of the variation in the MDR TB proportion p (figure 1). By grouping regions of the world that had similar MDR TB proportions, we were able to collapse the initial 8 regions to 3 that were significantly different from each other (χ^2 test). Group 1 included established market economies and Latin America. Group 2 comprised eastern Europe and the eastern Mediterranean and western Pacific regions. Other African and Southeast Asian countries were in group 3. The regression equation therefore was $\ln[p/(1-p)] = a_{1,2,3} + bG + cT$, where the intercepts $a_{1,2,3}$ for regional groups 1–3 were 1.373 (SE, 0.390), 2.095 (SE, 0.377), and 0.425 (SE, 0.309), respectively, and the regression coefficients were $b = -0.312$ (SE, 0.029) and $c = -0.037$ (SE, 0.004).

We calculated the total MDR TB cases as the product of p and the estimated TB incidence for each country [1, 4]. By application of the above equation, we show 106,630 new MDR TB cases for the 72 nonsurveyed countries (table 1). Summing for all 136 countries gave 272,906 new MDR TB cases in the year 2000. This is 3.2% (95% confidence limits [CLs], 2.6% and 3.9%) of the 8.4 million new TB cases arising that year, similar to the 3.4% obtained from the surveyed countries alone. The aggregate percentage is somewhat smaller because a disproportionate number of countries not yet surveyed are in Africa (group 3), where rates of resistance appear to be relatively low. Allowing for all 3 sources of error in computing the number of MDR TB cases gives approximate lower and upper 95% CLs of 184,948 and 414,295 new MDR cases.

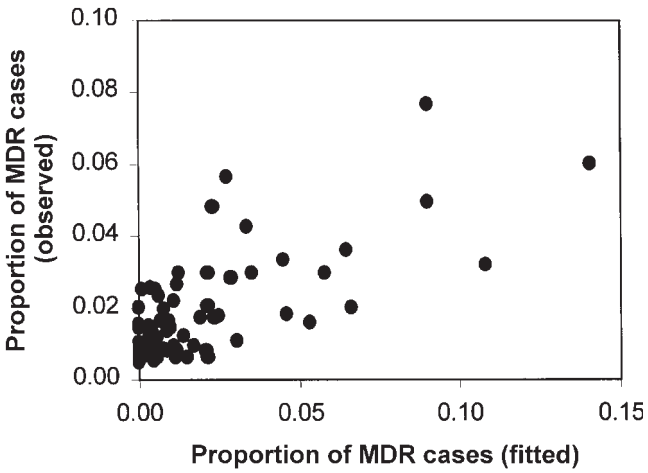

Figure 1. Goodness of fit of the logistic regression model as indicated by the correlation between the observed and predicted proportions of multidrug-resistant (MDR) tuberculosis cases in 64 surveyed countries.

Table 2. Estimated numbers and proportions of multidrug-resistant (MDR) tuberculosis (TB) cases in surveyed and nonsurveyed countries.

Country	No. of TB cases	No. of MDR TB cases	Low 95% CL	High 95% CL	MDR TB, %	Low 95% CL	High 95% CL
Surveyed							
Argentina	20,379	942	527	1505	4.6	2.9	6.3
Benin	16,575	50	<0	150	0.3	<0	0.9
Bolivia	19,166	231	38	445	1.2	0.2	2.2
Botswana	12,460	59	<0	130	0.5	<0	1.0
Brazil	115,983	1052	512	1740	0.9	0.5	1.3
CAR/Bangui	16,361	176	16	351	1.1	0.1	2.0
Chile	3763	15	<0	34	0.4	<0	0.9
China, Hong Kong	6311	88	57	136	1.4	1.1	1.7
China (DOTS[a])	650,502	18,520	11,305	28,936	2.8	2.0	3.7
China (non-DOTS[a])	650,502	49,844	34,515	75,216	7.7	6.3	9.0
Colombia	21,020	105	<0	315	0.5	<0	1.5
Cuba	1572	0	0	0	0.0	0.0	0.0
Czech Republic	1906	20	<0	45	1.1	<0	2.3
Denmark	682	3	<0	8	0.5	<0	1.2
Dominican Republic	12,470	823	418	1348	6.6	3.8	9.4
England/Wales	6947	55	29	89	0.8	0.5	1.1
Estonia	935	131	85	202	14.1	10.5	17.6
Finland	573	0	0	0	0.0	0.0	0.0
France	9074	0	0	0	0.0	0.0	0.0
Germany	10,088	90	36	155	0.9	0.4	1.4
Guinea	20,477	114	<0	254	0.6	<0	1.2
India	1,864,930	63,136	25,885	108,340	3.4	1.6	5.2
Iran	35,850	2074	1257	3248	5.8	4.0	7.5
Italy	5168	61	16	111	1.2	0.4	2.0
Ivory Coast	58,567	3111	1475	5178	5.3	2.9	7.8
Kenya	148,177	0	0	0	0.0	0.0	0.0
Latvia	2783	250	167	382	9.0	7.0	11.0
Lesotho	12,647	115	<0	256	0.9	<0	1.9
Malaysia	24,747	25	<0	75	0.1	<0	0.3
Mexico	37,630	901	244	1653	2.4	0.8	4.0
Morocco	33,504	723	263	1268	2.2	0.9	3.4
Mozambique	86,588	3032	1798	4774	3.5	2.4	4.6
Nepal	49,687	478	<0	1437	1.0	<0	2.8
Netherlands	1459	8	1	16	0.6	0.1	1.0
New Caledonia	186	0	0	0	0.0	0.0	0.0
New Zealand	225	3	<0	6	1.1	<0	2.7
Nicaragua	4294	53	12	100	1.2	0.3	2.2
Northern Ireland	526	0	0	0	0.0	0.0	0.0
Norway	221	5	<0	11	2.2	<0	4.6
Oman	229	2	<0	5	0.8	<0	2.2
Peru	54,310	1666	1068	2570	3.1	2.3	3.9
Poland	14,107	85	41	142	0.6	0.3	0.9
Portugal	5113	88	37	150	1.7	0.8	2.6
Puerto Rico	352	9	0	18	2.5	0.1	4.9
Republic of Korea	28,951	635	402	983	2.2	1.6	2.8
Romania	30,110	828	512	1289	2.8	2.0	3.5
Russia	97,223	5864	3761	9039	6.0	4.5	7.6
Scotland	604	2	<0	6	0.0	<0	1.0
Sierra Leone	13,592	116	<0	350	0.9	<0	2.5
Singapore	1704	5	<0	12	0.3	<0	0.7
Slovakia	1356	5	<0	11	0.3	<0	0.8
Slovenia	509	4	<0	9	0.7	<0	1.6
South Africa	215,943	3267	1098	5809	1.5	0.6	2.4
Spain	23,197	74	<0	222	0.3	<0	0.9
Swaziland	6145	55	<0	123	0.9	<0	1.9
Sweden	367	2	<0	5	0.6	<0	1.3

(continued)

Table 2. *(Continued.)*

Country	No. of TB cases	No. of MDR TB cases	Low 95% CL	High 95% CL	MDR TB, %	Low 95% CL	High 95% CL
Switzerland	640	0	0	0	0.0	0.0	0.0
Thailand	85,848	1812	964	2935	2.1	1.3	2.9
Uganda	77,125	412	<0	1015	0.5	<0	1.3
Uruguay	935	0	0	0	0.0	0.0	0.0
USA	15,123	183	129	275	1.2	1.0	1.4
Venezuela	10,132	0	0	0	0.0	0.0	0.0
Vietnam	150,929	3537	1559	5981	2.3	1.2	3.5
Zimbabwe	69,183	1330	541	2287	1.9	0.9	3.0
Nonsurveyed							
Afghanistan	72,915	5330	<0	13,520	7.3	<0	16.7
Algeria	14,451	98	<0	438	0.7	<0	1.6
Angola	35,694	827	<0	2599	2.3	<0	5.5
Armenia	2320	173	<0	863	7.5	<0	17.1
Australia	1505	16	<0	167	1	<0	2.5
Austria	1264	10	<0	121	0.8	<0	1.9
Azerbaijan	4958	246	<0	1064	5	<0	11.5
Bangladesh	308,271	4351	<0	11,217	1.4	<0	3.3
Belarus	8985	179	<0	746	2	<0	4.7
Burkina Faso	38,927	1013	<0	3078	2.6	<0	6.1
Burundi	27,663	860	<0	2746	3.1	<0	7.3
Cambodia	63,850	2698	<0	7265	4.2	<0	9.8
Cameroon	51,795	1252	<0	3611	2.4	<0	5.7
Chad	21,116	605	<0	2052	2.9	<0	6.7
Congo	10,132	141	<0	654	1.4	<0	3.3
DR Congo	168,189	2516	<0	6716	1.5	<0	3.5
Ecuador	22,212	887	<0	2890	4	<0	9.3
Egypt	26,368	1480	<0	4180	5.6	<0	13
El Salvador	4028	162	<0	857	4	<0	9.4
Eritrea	11,322	179	<0	824	1.6	<0	3.7
Ethiopia	252,381	5766	<0	14,809	2.3	<0	5.4
Gambia	3474	52	<0	366	1.5	<0	3.5
Georgia	3708	230	<0	1024	6.2	<0	14.3
Ghana	58,238	1533	<0	4344	2.6	<0	6.2
Guatemala	9676	168	<0	836	1.7	<0	4.1
Guinea-Bissau	3318	77	<0	488	2.3	<0	5.5
Haiti	28,744	1180	<0	3700	4.1	<0	9.6
Honduras	5877	147	<0	812	2.5	<0	5.9
Hungary	4155	248	<0	1068	6	<0	13.7
Indonesia	594,736	4030	<0	10,313	0.7	<0	1.6
Jamaica	198	4	<0	100	2	<0	4.8
Japan	35,734	278	<0	974	0.8	<0	1.8
Jordan	666	19	<0	200	2.8	<0	6.5
Kazakhstan	24,691	968	<0	2906	3.9	<0	9.1
Kuwait	607	20	<0	178	3.3	<0	7.8
Kyrgyzstan	7212	811	<0	2625	11.2	<0	25.1
Lao People's DR	9420	765	<0	2515	8.1	<0	18.5
Lebanon	736	25	<0	228	3.4	<0	7.9
Lithuania	4059	167	<0	760	4.1	<0	9.6
Madagascar	41,374	951	<0	2905	2.3	<0	5.4
Malawi	49,635	1039	<0	3138	2.1	<0	4.9
Mali	30,581	746	<0	2392	2.4	<0	5.7
Mauritius	801	3	<0	40	0.4	<0	0.9
Mongolia	5468	334	<0	1349	6.1	<0	14.1
Myanmar	76,621	1141	<0	3349	1.5	<0	3.5
Namibia	9133	270	<0	1163	3	<0	6.9
Niger	27,697	775	<0	2490	2.8	<0	6.6
Nigeria	343,017	5740	<0	14,647	1.7	<0	4
Pakistan	273,099	26,201	<0	62,249	9.6	<0	21.6

(continued)

Table 2. *(Continued.)*

Country	No. of TB cases	No. of MDR TB cases	Low 95% CL	High 95% CL	MDR TB, %	Low 95% CL	High 95% CL
Panama	1484	45	<0	380	3	<0	7.1
Papua New Guinea	11,993	919	<0	2842	7.7	<0	17.5
Paraguay	3624	114	<0	684	3.2	<0	7.4
Philippines	238,554	7642	<0	19,170	3.2	<0	7.5
Rwanda	31,833	617	<0	2036	1.9	<0	4.6
Saudi Arabia	9653	289	<0	1042	3	<0	7
Senegal	25,003	542	<0	1810	2.2	<0	5.1
Somalia	36,388	683	<0	2007	1.9	<0	4.4
Sri Lanka	11,004	114	<0	542	1	<0	2.5
Sudan	56,784	5712	<0	14,341	10.1	<0	22.6
Syrian Arab Republic	13,713	913	<0	2812	6.7	<0	15.3
Tajikistan	7151	407	<0	1555	5.7	<0	13.1
TFYR Macedonia	4771	210	<0	911	4.4	<0	10.3
Togo	14,811	344	<0	1310	2.3	<0	5.5
Trinidad and Tobago	165	4	<0	96	2.3	<0	5.4
Tunisia	3389	85	<0	475	2.5	<0	5.9
Turkey	24,110	1166	<0	3356	4.8	<0	11.2
Turkmenistan	4433	345	<0	1362	7.8	<0	17.7
Ukraine	39,769	3520	<0	9081	8.9	<0	20
UR Tanzania	122,480	1518	<0	4261	1.2	<0	2.9
Uzbekistan	26,090	1411	<0	4055	5.4	<0	12.5
Yemen	19,375	2408	<0	6431	12.4	<0	27.5
Zambia	49,308	908	<0	2761	1.8	<0	4.3

NOTE. CAR, Central African Republic; CL, confidence limit; DR, democratic republic; TFYR, The Former Yugoslav Republic; UR, United Republic.

[a] World Health Organization TB control strategy [3].

Established market economies in western Europe, North America, and Asia had < 1000 MDR TB cases in total, whereas Southeast Asia and the western Pacific regions each had > 75,000 (table 1). Few data are available from some large countries so estimates are subject to large random errors and probably systematic errors too. We calculated that India had 63,100 new MDR TB cases in 2000, 3.4% of all new cases. But the range is wide (25,900–108,300 cases) because this result is derived from a single survey of 384 patients in Tamil Nadu. The uncertainty may be greater if resistance rates are systematically higher or lower elsewhere in the country. For China, examination of 2918 patients in 4 provinces gave a nationwide estimate of 68,400 MDR TB cases (range, 45,800–104,200). The estimate for Russia, based on examinations of all patients (including prisoners) in 3 oblasts, was 5900 (range, 3800–9000) new MDR TB cases. Table 2 lists estimates for all 136 countries. Table 3 shows the distribution of surveyed and nonsurveyed countries among the 3 geographical groups and gives the regression statistics.

For countries where resistance surveys have not yet been done, the errors may be still larger. The most significant example is Pakistan (eastern Mediterranean region), for which the best estimate is 26,200 MDR TB cases but the upper 95% CL is 62,200. These uncertainties are also reflected in our estimates of MDR TB proportions. The highest were in the eastern Europe (5.5%) and eastern Mediterranean (7.9%) regions. The range for the latter is especially large (1.7%–14.1%) because there have been no surveys in the region's most populous countries, Afghanistan, Pakistan, and Sudan.

Discussion

A drug regimen to treat TB cases resistant to isoniazid and rifampicin, negotiated through the World Health Organization's Green Light Committee, is currently ~50 times more costly than the cheapest short-course regimen for drug-susceptible cases [7]. Even at this relatively favorable price, it could cost more to treat the 3.2% of new TB cases that are MDR than all other new TB cases together. Adding in the cost of managing MDR TB cases that have previously failed treatment would present a bill for drugs that is substantially greater. Because the proper

Table 3. Summary of data and regression statistics for surveyed and nonsurveyed countries.

Geographical group	Distribution of countries, %		Regression statistic (SE)[a]
	Surveyed	Nonsurveyed	
1	16.67	46.88	1.373 (0.067)
2	43.06	28.13	2.095 (0.043)
3	40.28	25.00	0.425 (0.088)
Mean ln GNP	8.06	6.62	− 0.313 (0.029)
Mean treatment success	79.01	73.67	− 0.037 (0.004)

NOTE. GNP, gross national product.

[a] Regression statistics for the 3 geographical groups are intercepts; for GNP and treatment success, they are slopes.

management of drug-resistant patients demands in many countries a significant fraction of the overall budget for TB control, we need precise estimates of the number and distribution of resistant cases.

Our analysis provides the first comprehensive set of estimates of MDR TB burden for the 136 countries that make up 97% of the world's population. The calculations are approximate—lower and upper bounds differ by a factor of about 2. However, both the size of the estimates and the uncertainty surrounding them point to the areas where resistance surveys are urgently needed. Countries that probably had >5000 new cases of MDR TB in 2000 and for which surveys are planned or are in progress include Ethiopia, Indonesia, Nigeria, the Philippines, and Sudan. Cambodia and Zambia have recently completed national surveys. Surveys are also planned or are underway in Bangladesh, China, Democratic Republic of Congo, Egypt, India, Mexico, Russia, South Africa, and Ukraine. These surveys will provide the data needed to narrow the bounds on the global estimate of MDR TB burden and, more importantly, to facilitate the effective planning of TB control within each of these countries.

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References

1. Espinal M, Simonsen L, Laszlo A, et al. Anti-tuberculosis drug resistance in the world. Report 2. Geneva: World Health Organization **2000**: 253.
2. Espinal M, Simonsen L, Laszlo A, et al. Global trends in resistance to antituberculosis drugs. N Engl J Med **2001**;344:1294–303.
3. World Health Organization. Global tuberculosis control. WHO report. Geneva: World Health Organization WHO/TB **2001**:287.
4. Dye C, Scheele S, Dolin P, Pathania V, Raviglione MC. Global burden of tuberculosis: estimated incidence, prevalence and mortality by country. JAMA **1999**;282:677–86.
5. World Bank. World development report: attacking poverty. New York: Oxford University Press, **2000**.
6. Crawley MJ. GLIM for ecologists. Oxford, UK: Blackwell Scientific Publications, **1993**.
7. Gupta R, Kim JY, Espinal MA, et al. Responding to market failures in tuberculosis control. Science **2001**;293:1049–51.